A direct comparison of decision rules for early discharge of suspected acute coronary syndromes in the era of high sensitive troponin

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Abstract

Background: We tested the hypothesis that a single high sensitive troponin at limits of detection [LOD](HSTnT)(<5ng/l)combined with a presentation non-ischaemic ECG is superior to low risk GRACE(<75),TIMI(≤1) and HEART score(≤3) as an aid to early,safe discharge for suspected ACS(acute coronary syndrome)

Methods: In a prospective cohort study,risk scores were computed in consecutive patients with suspected ACS presenting to emergency room (ER) of a large English hospital. Adjudication of MI,as per 3rd universal definition,involved 2 physician blinded, independent review of all biomarker positive chest pain re-presentations to any national hospital.The primary and secondary outcome was a composite of type 1 MI, unplanned coronary revascularisation and all cause death[MACE]at 6 weeks and 1 year.

Results: Of 3054 consecutive presentations with chest pain 1642 had suspected ACS(52% male, median age59,14% diabetic,20% previous MI).*Median time from chest pain to presentation was 9.7 hours.* Re-presentations occurred in 8 hospitals with 100% follow-up achieved.211(12.9%) and 279(17%) were adjudicated to suffer MACE at 6 weeks and 1 year respectively.Only HEART≤3(negative predictive value[NPV] MACE 99.4%, sensitivity 97.6%,%discharge 53.4) and LOD HsTnT strategy(NPV MACE 99.8%,sensitivity 99.5%, %discharge 36.9) achieved pre-specified NPV of >99% for MACE at 6 weeks.For type 1 MI alone the NPV at 6 weeks and 1 year was identical,for both HEART≤3 and LOD HsTnT at 99.8% and 99.5% respectively.

Conclusion:HEART ≤3 or LOD HSTnT strategy rules out short and medium term MI with ≥99.5% certainty,and short-term MACE with > 99% certainty allowing for early discharge of 53.4% and 36.9% respectively of suspected ACS. Adoption of either strategy has the potential to greatly reduce ER pressures and minimise follow-up investigations. *Very early presenters (<3 hours), due to limited numbers, are excluded from these conclusions.*

Key words: high sensitivity troponin, acute coronary syndromes.

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Abbreviations:

HSTnT= high sensitivity troponin T, MI= Myocardial Infarction, MACE: major adverse cardiac event (composite of type 1 MI, unplanned coronary revascularisation[surgical or PCI) and all cause death, ER= emergency room, CP= chest pain, NPV= negative predictive value. PCI= percutaneous coronary intervention, LOD= limits of detection, ACS= acute coronary syndrome

Introduction

Acute CP is one of the commonest presentations to ER in the Western world, the vast majority of which are not due to acute MI.[1,2,3,4] However early differentiation of type 1 MI from non-cardiac causes of troponin elevation remains a challenge despite the emergence of high sensitive troponins.[5] Early, safe discharge for a substantial proportion of chest pain presentations continues to be the single most important challenge, particularly for health care providers. Discharge at presentation with troponin [6 7] at the limits of detection [LOD] or early after a 1-hour high sensitivity troponin strategy remains an attractive proposition, [8 9] though there remains concerns about the sensitivity for rule-out of MI in the 1 hour algorithm particularly for early presenters.[9,10] It is not certain if these high sensitive troponin values, when combined with clinical assessment, ECG findings and risk factors improve early rule out. A number of risk scores which incorporate some or all of these factors have been in existence or been developed [11]to address this need but to date a high sensitive troponin strategy either alone or combined with risk scores as a tool for early discharge has not been tested prospectively in an **unselected**, **consecutive** chest pain population in whom there is suspicion of an underlying ischaemic cause.

We compared rule-out strategies; namely a single HSTnT (at limits of detection and at 99th percentile) combined with non-ischaemic ECG versus low score HEART (≤3), TIMI (≤1) and GRACE(<75) in an **unselected consecutive chest pain** patient population with suspected ACS. Our goal was to define the optimum rule-out strategy for suspected ACS using a single high sensitivity troponin T and presentation electrocardiogram.

Methods

This study was conducted in concordance with STARD criteria for diagnostic studies (score sheet included in appendix). From June 2011 to November 2011 all patients presenting to university hospital Aintree emergency department with a predominant symptom of chest pain, who had both an

electrocardiogram and at least one blood sample for HSTnT check (suspected ACS population), were prospectively 'recruited' into this study. Aintree university hospital is a large hospital providing secondary care cardiology with annual attendances of 80,000 per annum to accident and emergency. Prior to the start of the study there was a 3-month 'roll-in' phase with conversations between accident and emergency clinicians and the development of a chest pain proforma (acute chest pain assessment sheet) that highlights important aspects of history taking in chest pain as well as allowing capture of relevant information important in computation of the risk scores noted. Use of this proforma was not mandatory but was incorporated with casualty sheets as an aide memoire for clinicians for assessment of chest pain. Research personnel prospectively and contemporaneously entered demographic, epidemiological data and results of blood tests together with timing of ECGs and troponins in a dedicated database. All ECGS were stored in an electronic register for subsequent analysis by the research team. Each ECG was read by an experienced clinician/ researcher, with a second reading if there was troponin elevation to adjudicate if type 1 MI definition had been met. The presence and absence of specific criteria were noted electronically in a standardised fashion. The definition of a non-ischaemic ECG was the following: sinus rhythm or atrial fibrillation or atrial flutter with ventricular rate<110 together and **absence** of the following: LBBB, paced rhythm, ST segment elevation, ST segment depression, T wave inversion or T wave flattening or biphasic T waves in 2 contiguous leads. For both HSTn T LOD and non-ischaemic ECG strategy and the 3 risk scores the first(presentation) ECG alone was used as the ECG input variable. Subsequent ECGs were extracted for adjudication of MI and to determine possibilities of MI in those with a single sampled HSTn T.

TIMI and GRACE scores were determined from online calculators by research staff with the use of the CP proforma, casualty sheets and ambulance proforma alone. To score positively for ST segment depression in GRACE and TIMI planar depression of at least 0.5mm after the J-point consistent with the Minnesota criteria. [12]

There was no specific troponin testing protocol for clinicians during recruitment. Guidelines recommended repeat troponin sampling for patients who presented <6 hours from chest pain particularly if presentation HSTnT was <99th percentile (<15ng/l). Discharge at <6 hours from chest pain with 'negative' troponin (HSTnT<15ng/l) was discouraged.

Calculation of HEART score, follow-up, definition and adjudication of MACE events (and nonischaemic diagnoses)- see appendix

High sensitivity cardiac troponin T assay

The assay used was the high sensitivity troponin T (Roche Elecsys). This has been previously evaluated extensively and found to fulfil the definition of high sensitivity with 10% coefficient variation at the 99th percentile. [16] Performance of this assay across a number of centres has previously been evaluated. [16] Analysis was undertaken in-house of COBAS e601 analysers using a standard 18-minute assay. Quality control of assay (in-house) at Liverpool Clinical laboratories revealed a coefficient of variation of 11% at low value troponins (<10ng/l). External quality assurance provided by the independent United Kingdom National External quality assurance scheme (NEQA) revealed inter-hospital coefficient of variation of 10% (standard deviation 0.5) low level Troponin values. Assay performance (NEQA) was undertaken monthly throughout the duration of the study.

During recruitment of the study there was a downward shift in the ROCHE elecsys HSTn T that was a result of calibration of specific LOTS.[17] We recomputed HSTnT values by adjusting for the shift by reference to local laboratory calibration and that determined by a number of groups including the manufacturer. [17,18] The adjusted or recomputed values that were used in the analysis.

End-points

The primary endpoint was type 1 MI, unplanned coronary revascularisation and all cause death (MACE)at 42 days (see appendix for definitions and adjudication). Unplanned coronary revascularisation

was defined **as admission for unstable angina or MI necessitating same day or same admission coronary revascularisation by percutaneous or surgical means**. Secondary endpoint included MACE at 1 year

Ethics

This manuscript conforms to the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals,

This was an all-comers chest pain study with national(English) hospital involvement for any representation with possible MI. The project was registered with the hospital research department and the regional ethics board which granted full consent to undertake this study. (north-west England regional ethics board) To allow for complete follow-up special permission was granted, in the absence of individual consent, via a confidential advisory group(UK government home office appointed) for the recruitment of consecutive CP population and collection of data from any hospital nationwide to facilitate the retrieval of clinical records and blood results for patients with possible acute coronary syndrome. (15/CAG/0171) [http://www.hra.nhs.uk/]

Statistics

All analyses were performed in Stata v14.

Summary statistics were presented as n(%) if categorical and as median(IQR) if continuous. For categorical variables, a Pearson $\chi 2$ test was used to determined p-value, except for cases where there were number of MACE events in any category was ≤ 5, when Fisher's Exact test was used. For continuous variables, a t-test was performed to determine p.

Confidence intervals for PPV and NPV were calculated using exact binomial proportions.

To evaluate differences in NPV in patients who had their first HSTnT at ≤3hrs and ≤6hrs compared to those >3hrs and >6hrs, P-values were computed using a 2-sided Fisher's Exact Test.

ROC curves were plotted, and area under curve (AUC) computed, using the rocreg function in Stata to bootstrap and obtain standard errors and confidence intervals. The p-value for differences in the AUC was obtained using a Wald test.

It was not possible to compute an exact sample size at the time of recruitment as we had no information on events rates for HSTnT LOD at the time of starting the study or indeed good evidence of event rates for risk scores with high sensitivity troponins.

Results

Figure 1 charts the global chest pain population and those with suspected ACS(defined as sampling of HSTnT together with presentation electrocardiogram). Missing data (loss of casualty cards and incomplete/ illegible CP proforma) was <1.2% of the global population. Follow-up was 100% with tracking of repeat presentations to ER/ admissions to 8 national hospitals (table 3 appendix). Retrieval of all necessary reports, blood results, ECGs, relevant imaging reports, for all patients that had biomarker positive presentations was achieved for the purposes of adjudication of MI.

Table 1 describes the characteristics of all patients (both those admitted and directly discharged from accident and emergency department). It further subdivides the population into those adjudicated to have suffered type 1 MI and MACE at 6 weeks. 444 patients (27%) were discharged directly from accident and emergency at a median of 363 minutes (IQR range 271, 468minutes). Four of these patients suffered MACE by 6 weeks (0.9%) (3 were adjudicated to fulfil definition of type 1 MI at index admission [ie wrongly discharged]). The decision to admit or discharge was at the discretion of clinicians (at the time no specific protocol or risk score was in place to guide clinicians). Those adjudicated to have suffered a MACE events (type 1 MI, all cause death, unplanned coronary revascularisation) were older with greater

risk factors. Risk scores were consistently higher for all patients with type 1 MI or MACE at 6 weeks There were 10.7% of patients adjudicated to have suffered a type 1 MI at index admission with another 0.3% between admission and 6 weeks at a median of 11 days following admission. The percentage of patients undergoing unplanned PCI and unplanned CABG up to 6 weeks were 2.7% and 0.8% respectively at a median of 7 and 18 days following admission. The number of patients undergoing emergency primary percutaneous coronary intervention for ST elevation myocardial infarction up to 1 year who were discharged with a diagnosis other than ACS was 4(0.2%) at a median of 80 days following discharge. The number of deaths at 6 weeks and 1 year were 25(1.5%) and 104(6.3%) respectively occurring at a median of 15 and 112 days respectively. Of the total deaths at 1-year 11% were in-hospital and 89% out of hospital. The overall type 1 MI and MACE event rate at 6 weeks was 11.2% and 12.9% respectively. For 1 year, the equivalent figures for type 1 MI and MACE were 11.6% and 17%. For the entire population diagnoses other than type 1 MI were the following: type 2 MI 1.2%, unstable angina 8.5%, atypical chest pain 8.5%, cardiac noncoronary chest pain 7.9%, non-cardiac symptoms 57.2%, CP unknown origin 2.8%. (see appendix for prespecified criteria)

Table 2 demonstrates performance of the rule out protocols at 6 weeks and 1 year for MACE and type 1 MI. Only HEART ≤3 and LOD HSTn T(with non-ischaemic ECG) achieved the prespecified NPV of >99% at 6 weeks for MACE (NPV with prespecified 99% performance target represented graphically in figure 1 appendix). The discharge potential for these strategies were 53.4% and 36.9% for HEART≤3 and LOD HSTn T(with non-ischaemic ECG) respectively. They achieved sensitivities for MACE of 97.6% and 99.5% for HEART ≤3 and LOD HSTn T(with nonischaemic ECG) respectively. For Type 1 MI alone as an endpoint the respective figures for sensitivity were 98.9% (HEART≤3) and 99.4%(LOD HSTn T and nonischaemic ECG). The respective NPV at 6 weeks for type 1 MI for LOD HSTn T and HEART≤3 was identical at 99.8%. At 1 year point estimates of NPV (99.5%) for type 1 MI was again identical for HEART≤3 and HSTnT LOD. In terms of overlap between LOD HSTn T with nonischaemic ECG and

HEART≤3, 521/606 (86.0%) of patients fulfilling discharge rules with LOD HSTN T + nonischaemic ECG also had a HEART score of ≤3. The equivalent percentage for the reverse was 59.4% ie 59.4% with HEART score ≤3 had a LOD HSTNT.

In terms of NPV for MACE events LOD HSTn T and non-ischaemic ECG was clearly differentiated from HSTn T ≤14ng/l (99^{th} percentile value)(with nonischaemic ECG) and TIMI ≤1 but not GRACE <75 or HEART ≤3. GRACE <75, in terms of discharge potential, could deliver only 28.6% discharges (similar to actual direct discharge of 27% in this cohort)

Table 1 (appendix) details patients with HEART ≤3 and LOD HSTnT and non-ischaemic ECG with MACE events (the false negative population or those fulfilling rules for discharge but who had an adjudicated MACE). All 3 deaths ≤ 6weeks from index event, that represented 3 of the 5 false negative events for patients with HEART ≤3, were clear noncardiac deaths. The performance of HEART≤3 was considerably improved by not counting non-cardiac deaths as events. Sensitivity improved to 99% with NPV to 99.8% for MACE at 6 weeks. For patients with a first HSTnT LOD (<5ng/L) there were 2 patients with a 2^{nd} troponin >14ng/l, both of which were adjudicated as suffering type 1 MI(only one of which had a non-ischaemic presentation ECG).

Figure 2 describes ROC(receiver operator characteristic) curves for continuous values of risk scores and with HSTnT being analysed without ECG interpretation as a continuous variable. Compared to HSTnT(ROC area 0.918) there was no significant difference in performance with HEART(ROC area 0.910, p<0.382) but there was significant separation of curves with TIMI(ROC area 0.855, p<0.001) and GRACE(ROC area 0.791,p<0.001). Figure 2 (appendix) describes time of chest pain to first HSTnT samples.

57% of patients had 1 HSTnT sampled. 51.9% of patients had >1 ECG (median time to first and 2^{nd} ECG 10mins, [IQR 5,15mins] and 181 mins, [IQR 69,414 mins]). To determine the possibility of missed MI

due to single HSTnT<14ng/l we re-evaluated paired ECGs to determine if there were dynamic ECG changes(a significant change such as new t wave inversion, ST segment shift, development of LBBB). in those with a single HSTN T Only 3 patients with a single HSTnT had a dynamic change in ECG but in only one was a type 1 MI adjudicated (2nd ECG demonstrated STEMI). His initial ECG though was not normal thus excluding a false negative result for HEART ≤3 and HSTn T LOD (presentation HSTnT<5ng/l).

Sensitivity Analysis

A sensitivity analysis was undertaken with GRACE values of <60 and <90 and TIMI score 0 and ≤2 for MACE at 42 days.

GRACE score <60 did achieve NPV of 99.6% with a sensitivity of 99.5% but percentage discharge dropped to 14.3%. GRACE score <90 did not achieve prespecified thresholds of NPV (NPV 97.2%) with a sensitivity of 90.5%. TIMI score 0 did achieve threshold NPV of 99.7% with a sensitivity of 99.1% and allowed discharge of 39.1% patients. TIMI score ≤2 allowed discharge of 74.1% but at a considerable loss of sensitivity and NPV of 73% and 95.3% respectively.

Inter-observer variability of determination or Risk scores

Absolute agreement for risk scores was were good for HEART and TIMI and excellent (100%) per risk category (K=1). No patients were categorised as high or intermediate risk that were initially deemed low risk (and vice versa) for HEART and TIMI scores. GRACE scores in terms of absolute agreement performed less well but still very good for risk category agreement (K=0.82). (table 4 appendix)

Discussion

We confirm the impressive rule-out strategy of HSTnT using limits of detection (or limit of blank alone<3ng/l) [6,7,19] combined with an non-ischaemic ECG. We have prospectively validated the 2 cornerstones in acute CP assessment, (namely troponins and ECG) as a simple and effective strategy for decision making with very low risk of adverse outcome. Rubini-Gimenez et al identified the potential of rule-out value of undetectable HSTN T and I. [6] Mokhtari et al further demonstrated incremental value of the combination of HSTn T LOD, nonischaemic ECG and low risk history but in a non-consecutive patient series.[20] As far as we are aware this is the only study that has **prospectively** assessed HSTn T at LOD and non-ischaemic EC) in an **unselected, consecutive** chest patient population. Our point estimate of NPV are similar to that of Bandstein et al[7] and Body et al [19] even though a lower limit of blank (<3ng/l) was used in the latter study.Sandoval et al define the concept of LOD and LOB as rule out strategies. [21] The LOD provide higher NPV and sensitivities than that of Rubini-Gimenez et al.[6] Incorporation of a non-ischaemic ECG to the limits of detection of HSTnT could explain this; LOD HSTnT together with nonischaemic ECG increased sensitivity from 98.1% to 99.5% for MACE and 98.9% to 99.4% for type 1 MI at 6 weeks (table 2).

This study is the first to demonstrate that HEART score≤3 in the era of high sensitive troponins (using conventional cut-offs of HSTnT) also, to a large extent, meets criteria for a rule-out strategy. HEART≤3 was as effective as LOD HSTn T with a non-ischaemic ECG) for rule-out of type 1 MI at 6 weeks with NPV of 99.8% with a sensitivity of 98.9% allowing a discharge of 53.4% of patients(as opposed to 36.9% of patients with LOD HSTnT strategy). The performance of HEART ≤3 for type 1 MI is indicative of an acceptable risk for a discharge/ rule out for type 1 MI. [22]In terms of MACE sensitivity was <98% but improved to 99% (at 6 weeks if only cardiac deaths were counted)

In addition this study have demonstrated that both rule-out strategies (HEART ≤3 and LOD HSTnT) have low event rates to 1 year for type 1 MI(99.5% at 1 year) indicating patients can be safely discharged and reassured without the need for early diagnostic testing in the absence of ongoing symptoms. This study suggests cardiac imaging for LOD HSTNT or low risk HEART score cannot seek to refine risk further and argues for a reduction to these requests in low risk patients.

TIMI score≤1 and GRACE score<75 did not reach prespecified thresholds for rule-out. Although neither of these risk scores had been originally validated for suspected ACS, they have been evaluated with encouraging results in combination with high sensitive troponins in a number of different protocols in chest pain populations. [232425] Sensitivity analysis revealed that TIMI score of 0 had acceptable performance but discharged considerably less than HEART≤3. (39.5%vs 53.4%)

A consecutive, unselected series of suspected ACS presentation, in a sample size this large, is important in terms of generalisability and therefore potential influence to change practise (as opposed to a selected population, a natural consequence of consent and limited or absent recruitment nocturnally or at weekends). There was 100% follow-up tracked nationally and there was adjudication of any index CP or representation with HSTn T that was above the 99th percentile. This allowed us not only to validate those coded for type 1 MI but to evaluate all patients with elevated troponins including those who were deemed to have noncardiac pathologies (a distinction from other noted studies). [7] Secondly we used all-cause death as an outcome rather than cardiac death as incorporated in some studies.[3]This is not to say that high sensitivity troponin can predict noncardiac death but to accept the uncertainty of cause of death, particularly for out of hospital deaths and the probability of misdiagnosis and therefore miscoding of cause of death. [26]Using all-cause death grants a safer estimate of rule-out protocols.

Recently Carlton et al directly compared risk scores using HSTn T and I in a select patient population of patients ≤80 years of age.[27] In a post-hoc analysis HEART ≤3 did not achieve pre-specified targets of >99.5% NPV and/or sensitivity of >98% with either HSTn T or HSTn I. Differences in study population

could explain this; Carlton et al had a population with much shorter time of CP to presentation which is likely to have reduced both NPV and sensitivity for HEART≤3.

The largest study to date in a population of all-comers similar to ours was that by Shah et al.[3] The impressive NPV of 99.6% (high sensitive troponin I- Abbot) with both a derivation and validation cohort fulfilled criteria for safety and clinical utility (almost 2/3rd could be discharged). However, there was no reported sensitivity as far as our group could discern. NPV is affected by disease prevalence rates thus highlighting the attractiveness of risk scores such as HEART which to some extent incorporate this aspect allowing potential widespread applicability of rule-out strategies for suspected ACS. Multicentre validation studies, preferably with studies enriched with early presenters, and with competitor high sensitivity troponin assays incorporated in HEART are important to confirm (or refute) the potential of the HEART score as a tool for rule-out of ACS.

In a previous study by Backus et al investigating the same risk scores in 2338 suspected ACS in a multicentre observational study revealed superiority of HEART compared to TIMI and GRACE across all risk categories but there was a 1.7% MACE event at 6 weeks with HEART≤3 with 4th generation (non-high sensitivity) troponins. This event rate would not be acceptable strategy as a rule-out in most health care systems.[3] High sensitivity troponins are likely to have improved sensitivity or rule-out value at the expense of reduced specificity.

Limitations

Figure 2 (appendix) demonstrates time from chest pain to first HsTn T check.Only 4.4% of patients had a HSTn T check <3 hours (very early presenters) from chest pain.The equivalent number for ≤6 hours was 240 (14.6%).There was no significant difference in NPV between those with ≤6 hours and the global population when incorporated in a troponin and ECG strategy or as low risk scores. (table 5 appendix). However these results should be treated with caution due to the low number of events occurring in

patients presenting early. Most CP presentations to ER are late, and the study does represent comparable numbers of patients with very early (≤3hours)[3] and early presentations (≤6hours)[7] to similar 'all-comer' studies. This study does not validate discharge for very early presenters, based on a single HSTnT.

43% patients underwent serial troponins. As a rise or fall in troponins or biomarkers of myocyte necrosis is part of the universal definition of MI we cannot be certain that MIs were not missed although most presentations are late (median time from CP to presentation 9.6 hours) thus reducing the possibility of a later rise of HSTn T beyond 99th percentile. Furthermore analysis of paired ECGS, in those with a single HSTnT sampled,for sequential ECG changes only revealed one definite MI (evolving ECG changes from t wave inversion to STEV).

There was a downward shift seen with this ROCHE assay between 2010 and 2012. [28] The actual difference computed between affected lots and correct (re-assayed) values was 1.2ng/l in a similar population of suspected acute coronary syndrome.[18] Wildi et al suggested a small miss rate with LOD HSTnT in affected lots compared to corrected values with serial samples and re-adjudication for MI. However 2 other analyses suggest similar prevalence rates of MI and no 'missed' MI with LOD initial samples when ECG ischaemia was taken into account. [29] Body et al using LOD revealed 2 missed MIs using paired samples in 463 patients with affected lots with retesting, but both patients had ischaemic ECGS maintaining NPV at 100%. In addition ROCHE internally assessed the effect of affected lots with readjustment mathematically in 1033 patients presenting to ER.[28] The identical number of MIs were defined.

Finally HEART score was not determined by attending physicians but researchers following presentation raising concerns about scoring chest pain section of HEART. However due both to engagement and the production of a tick box chest pain proforma that emphasises character and duration of CP it was always possible to score chest pain with reasonable reflection of clinician suspicion.

Conclusion

Heart ≤3 and LOD HSTnT (combined with a non-ischaemic ECG) are optimum rule-out strategies for MACE at 6 weeks, for a suspected ACS population. Further multicentre studies should test HEART ≤3 as a tool for early, safe discharge of patients with chest pain and suspected ACS particularly in early presenters. A randomised trial of LOD HSTnT versus a 1 hour HS troponin protocol decision rule to assess duration of stay and safety endpoints is urgently needed.

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Figure Legends

Figure 1: Flowchart of final population

Figures 2: ROC (receiver operator characteristics) curve for primary outcome (MACE) at 6 weeks

Appendix figures

Figure 1: Negative and Positive predictive values for MACE (type 1 myocardial infarction, unplanned coronary revascularisation and all cause death) at 42 days according to rule-out protocols

Figure 2: Time of chest pain to first High sensitivity troponin check

Table 1 Population characteristics

		All	Type 1 MI (6 weeks)	MACE (6 weeks)	P value
Totals		1642	180	211	
Age (median[IQR])		59(47,72)	74(62,82)	74(62,82)	<0.001
		N	**N**	**N**	
Sex: (Male)		858(52%)	109 (61%)	127(60%)	0.015
Risk Scores	**TIMI (MEAN, sd)**	1.50 (1.58)	3.47 (1.36)	3.38 (1.38)	NA
	HEART (mean, sd)	3.50 (2.30)	6.93 (1.61)	6.72 (1.71)	
	GRACE (mean, sd)	101.5 (39.6)	136.4 (32.1)	136.7 (35.7)	
Hypertension		695(42%)	121 (67%)	140 (66%)	<0.001
Smoking*	**Current**	457(28%)	42 (23%)	50 (24%)	0.005
	Previous	463(28%)	68 (38%)	82 (39%)	
	Never	589(36%)	59 (33%)	66 (31%)	
Diabetes mellitus		237(14%)	44 (24%)	55 (26%)	<0.001
Dyslipidaemia		432(26%)	75 (42%)	82 (39%)	<0.001
Family History of premature CAD^		337(21%)	34 (19%)	37 (18%)	0.302
Previous MI		322(20%)	65 (36%)	72(34%)	<0.001
Previous PCI		170 (10%)	32 (18%)	36 (17%)	0.001
Previous CABG		91 (6%)	21 (12%)	22 (10%)	0.001
Previous stroke		118(7%)	22 (12%)	29 (14%)	<0.001
History of AF		164(10%)	29 (17%)	36 (17%)	<0.001
Hb (median(IQR)) g/dl		13.7(12.5,14.8)	13.0(11.7,14.4)	12.9(11.7,14.3)	0.023
MCV (median (IQR)) femtolitres		88.7(85.6,92.0)	89.6(86.1,92.7)	89.3(85.5,92.5)	0.780
Creatinine [median, IQR) mmol/l		91(79,105)	98(86,116)	97(84,118)	<0.001
C- reactive protein (median, IQR) mg/dl		4(4,9)	4(4,10)	4(4,13)	0.03
Systolic BP (median(IQR)) mmHg		131(118,146)	139(122,152)	136(121.151)	0.001
Heart Rate (median, IQR) {beats/min}		78(67,90)	77(66,88)	77(66,90)	0.89
CP onset/peak to presentation (median, IQR) hours		9.7(2.4,48.0)	4.2(1.6,15.7)	4.6(1.7,18.6)	<0.001
Time of chest pain^{+} to presentation					<0.001
	<6hrs	682(42%)	98 (56%)	111 (55%)	
	≥6hrs	946(58%)	73 (42%)	90 (43%)	
CP onset/peak to first troponin check (median, IQR) hours		14.0(6.8,49.0)	8.6(6.2,18.7)	9.2(6.2,21.0)	<0.001
Time of peak CP to first troponin					0.001
	≤6hrs	240(15%)	40 (22%)	47 (22%)	
	>6hrs	1389(85%)	136 (75%)	159 (75%)	
ECG Ischaemic∞		463(28%)	107 (59%)	123 (58%)	<0.001
ST depression ≥0.5mms		90(5%)	33 (20%)	37 (18%)	<0.001
T wave pathology					<0.001
	Nil	1262(77%)	93 (52%)	113 (54%)	
	Flat	73(4%)	12 (7%)	13 (6%)	
	Biphasic	31(2%)	11 (6%)	14 (7%)	
	Inverted	274(17%)	64 (36%)	71 (34%)	
Current aspirin use		491(30%)	86 (48%)	99 (47%)	<0.001

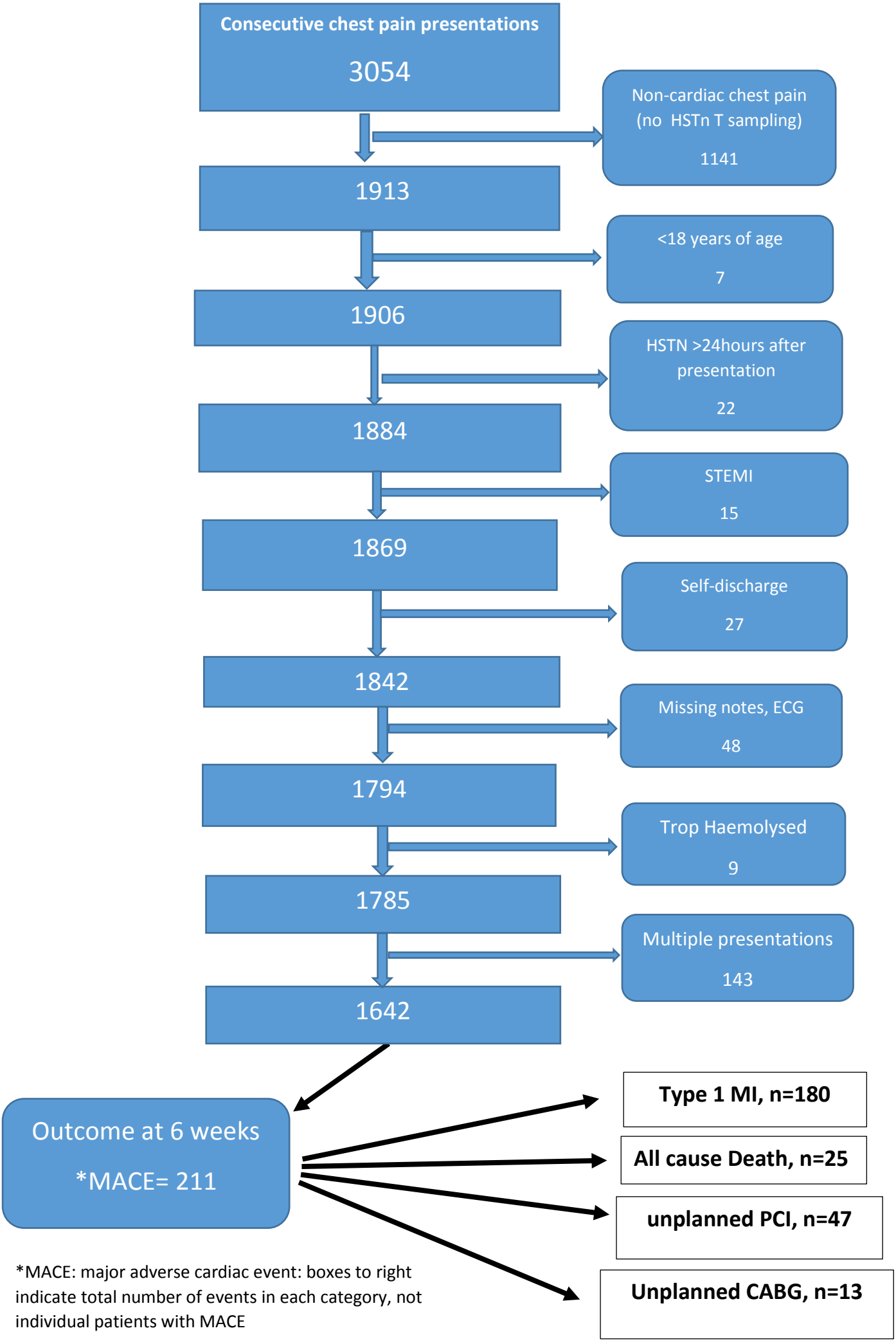
*Ie not known smoking status in 8%, ^ not known in 32%, + timing of chest pain uncertain in 1%, ∞ ischaemic ECG was defined as the following: rhythm other than sinus rhythm or AF/flutter with heart rate >110bpm, LBBB, paced rhythm, ST segment elevation, ST segment depression, T wave inversion or T wave flattening or biphasic T waves in 2 contiguous leads

Table 2: Performance of rule-out protocols for type 1 myocardial infarction and MACE at 6 weeks and 1 year

MACE (type 1 Myocardial Infarction, unplanned coronary revascularisation and all cause death)									
Rule-out protocol	**Discharge potential(%)**	**6 weeks**				**1 year**			
		PPV (95% CI)	**NPV (95% CI)**	**Sensitivity (95%CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**Sensitivity (95%CI)**	**Specificity (95% CI)**
TIMI ≤ 1	56.7	0.270 (0.238, 0.304)	0.980 (0.968, 0.988)	0.910 (0.863,0.945)	0.637 (0.612,0.662)	0.339 (0.304,0.375)	0.959 (0.944,0.971)	0.864 (0.818,0.902)	0.655 (0.629,0.680)
GRACE <75	28.6	0.172 (0.151, 0.195)	0.981 (0.964, 0.991)	0.957(0.921, 0.980)	0.322 (0.298,0.347)	0.229 (0.205,0.254)	0.977 (0.958,0.988)	0.961 (0.931,0.980)	0.336 (0.311,0.362)
HEART ≤ 3	53.4	0.269 (0.238, 0.302)	0.994 (0.987, 0.998)	0.976 (0.946,0.992)	0.609 (0.584,0.635)	0.331 (0.297,0.365)	0.970 (0.957,0.981)	0.907 (0.866,0.938)	0.624 (0.598,0.650)
HSTnT<5ng/l, ECG non-ischaemic	36.9	0.203 (0.179, 0.228)	0.998 (0.991, 1.000)	0.995 (0.974,1.000)	0.423 (0.397,0.449)	0.259 (0.232,0.286)	0.982 (0.968,0.991)	0.961 (0.931,0.980)	0.437 (0.410,0.463)
HSTnT<15ng/l, ECG non-ischaemic	59.4	0.291 (0.257, 0.327)	0.983 (0.972, 0.990)	0.919 (0.874,0.952)	0.669 (0.644,0.694)	0.360 (0.323,0.398)	0.960 (0.946,0.971)	0.860 (0.814,0.899)	0.687 (0.661,0.711)
HSTnT<5 ng/l alone	43.3	0.222 (0.196, 0.250)	0.994 (0.986, 0.998)	0.981 (0.952,0.995)	0.494 (0.468,0.520)	0.282 (0.254, 0.313)	0.977 (0.964, 0.987)	0.943 (0.909,0.967)	0.510 (0.483,0.537)
Type 1 Myocardial infarction									
Rule-out protocol	**Discharge potential(%)**	**6 weeks**				**1 year**			
		PPV (95% CI)	**NPV (95% CI)**	**Sensitivity(95%CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**Sensitivity (95%CI)**	**Specificity (95% CI)**
TIMI ≤ 1	56.7	0.232 (0.201, 0.265)	0.984 (0.974, 0.991)	0.917 (0.866,0.953)	0.627 (0.601,0.651)	0.245 (0.214, 0.278)	0.982 (0.971, 0.989)	0.911 (0.861,0.947)	0.630 (0.604,0.655)
GRACE <75	28.6	0.149 (0.129, 0.171)	0.989 (0.975, 0.997)	0.972 (0.936,0.991)	0.318 (0.294,0.342)	0.158 (0.137, 0.180)	0.987 (0.972, 0.995)	0.969 (0.933,0.988)	0.319 (0.295,0.344)
HEART ≤ 3	53.4	0.233 (0.203, 0.264)	0.998 (0.992, 1.000)	0.989 (0.960,0.999)	0.598 (0.573,0.624)	0.244 (0.214, 0.277)	0.995 (0.988, 0.999)	0.979 (0.947,0.994)	0.602 (0.576,0.627)
HSTnT<5ng/l, ECG non-ischaemic	36.9	0.173 (0.150, 0.197)	0.998 (0.991, 1.000)	0.994 (0.969,1.000)	0.414 (0.388,0.440)	0.181 (0.158,0.206)	0.995 (0.986, 0.999)	0.984 (0.955,0.997)	0.416 (0.390,0.441)
HSTnT<15ng/l, ECG non-ischaemic	59.4	0.250 (0.218, 0.285)	0.987 (0.977, 0.993)	0.928 (0.880,0.961)	0.658 (0.633,0.682)	0.261 (0.228, 0.296)	0.983 (0.972, 0.990)	0.911 (0.861,0.947)	0.660 (0.635,0.685)
HSTnT<5ng/l alone	43.3	0.191 (0.166, 0.218)	0.997 (0.990, 1.000)	0.989 (0.960,0.999)	0.485 (0.459,0.511)	0.201 (0.176, 0.228)	0.994 (0.986, 0.998)	0.979 (0.947,0.994)	0.487 (0.461,0.513)

Abbreviations: MACE= major adverse cardiac event, NPV= negative predictive value, PPV= positive predictive value. HSTnT= high sensitivity troponin T

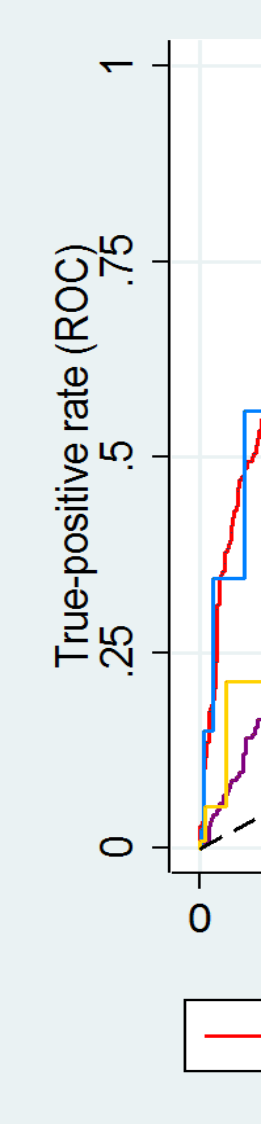
Figure 1: Flowchart of final population



*MACE: major adverse cardiac event: boxes to right indicate total number of events in each category, not individual patients with MACE

Figure 2: ROC (receiver operator characteristics) curve for primary outcome (MACE) at 6 weeks

ROC curves for risk scores (continuous) and high sensitive troponin T (HsTn T is a continuous variable without ECG criteria)



Area under curve: HSTnT 0.918, HEART 0.910, TIMI 0.855 [p<0.001 cf to HSTnT], GRACE 0.791[p<0.001 cf to HSTnT]

A direct comparison of decision rules for early discharge of suspected acute coronary syndromes in the era of high sensitive troponin

Chew P, Khand A et al

Calculation of the HEART score

The character of CP was scored exclusively on the narrative in the admission documentation and/or chest pain proforma. A score of 2 was ascribed when chest pain had documented features suggestive of cardiac chest pain and an absence of non-specific features. A score of 1 was given if there was combination of suspicious and non-specific symptoms and a score of 0 was given if there were only non-specific features. Researchers were prompted to grant high suspicion (a score of 2) if there was central chest pain with at least one additional feature such as radiation to the arm/ neck/jaw or sweating or relief with GTN or provocation of chest pain with exertion or emotion/stress. Admission ECGs were reviewed and ascribed a score of 2 in the presence of ST depression ≥0.5mm and 1 in the presence of bifid or inverted T waves or flat T waves in at least 2 contiguous leads of a 12 lead ECG. LBBB and paced rhythm were given a score of 1. Age categories were as per the HEART score. Risk factors considered were hypertension, smoking (current or ex-smoker <1 year), diabetes mellitus, hypercholesterolemia, positive family history and previous history of confirmed atherosclerotic coronary (this latter group included previous MI, CABG, percutaneous coronary intervention, cerebrovascular disease and stroke). We did not have consistent information on body weight and therefore were unable to score BMI>30 as a risk factor in HEART. The presence of ≥3, 1-2 and 0 risk factors for coronary artery disease scored 2,1 and 0 respectively (Confirmed atherosclerotic disease was attributed a score of 2 even in the absence of other risk factors).. A score of 0 was ascribed with HSTnT values of<15ng/l, values between 15 and 41ng/l a score of 1 was given and 2 for values >42. This is consistent

with HEART with scores dependant on 99th percentile of troponins in the reference population (0≤99th percentile, 1 for 99th percentile to 3X 99th percentile and a score of 2 for >x3 99th percentile).[11]

To ascertain inter-observer variability of risk score determination 2 researchers (AK and FF) undertook blinded assessment and repeat computation of risk scores of a random selection of 18 presentations with suspected ACS.

Follow-up

All clinicians were blinded to outcome of patients (except for inpatient death or death during subsequent admission). However, they could be aware of presentation troponins.

Patients were tracked by a linked national database by their NHS number (these are 16 digit codes and act as unique identifiers to any hospital in England). Codes for readmission were for any chest pain code or any code for ischaemic heart disease or for any coronary revascularisation (PCI or CABG) – see appendix (table 2 for list of codes). Deaths were tracked via the national mortality database. There were 30 patients without NHS numbers. For these patients to ascertain outcome we systematically contacted their general practitioners and the records department of 5 hospitals in the Cheshire and Mersey region (comprising a catchment population of 2.1million). All analyses for outcomes were independently undertaken by the statistician with outcomes spreadsheet and index presentation/ risk scores linked by a unique patient identifier only.

Adjudication of type 1 myocardial infarction/ MACE

For all index presentations 2 research clinicians independently reviewed all cases where at least one HSTn T was above 99th percentile (ie 14ng/l). All investigations including serial

ECGS, echocardiograms, other imaging investigations and angiograms up to 6 weeks from index admission were scrutinised to determine if a definition of type 1 or 2 MI was met. For index admission 2nd adjudicator was not blinded to the adjudication/ diagnosis of the first (unblinded). Disagreements were resolved by adjudication by a consultant cardiologist experienced in endpoint definition in clinical studies. For all possible re-infarctions (patients who had a further episode of chest pain with repeat HSTnT sampling outwith the initial sampling period) following presentation and representations with chest pain to any English hospital (appendix table 3 appendix) up to 1 year from discharge were selected (table 2 for ICD 10 codes used). The presence or absence of biomarker elevation (according to local laboratory reference range) was determined. In case of biomarker elevation independent and blinded (to index event and risk scores) adjudication was undertaken by 2 experienced clinicians (with a 3rd involved for divergences in adjudication). The criteria for defining MI, for both index admission events and readmissions, was based on the 3rd universal definition for MI. [13]Adjudicators were recommended that 50% rise or fall in a 2nd troponin was confirmatory of MI but 20-50% rise or fall was suggestive particularly in the context of convincing ischaemic symptoms or other corroborating evidence.

Type 2 MI was defined as evidence of myocardial ischaemia with myocyte necrosis but associated with an imbalance in supply and demand such as tachydysrhythmia, profound anaemia, hypotension. Agreement between clinicians for the presence or absence of myocardial infarction (repeat presentation with biomarker elevation) was 85%, K=0.58.

For patients who had multiple repeat presentations with chest pain the first presentation was assessed for biomarker elevation and/ or adjudication for type 1 MI. If type 1 MI was confirmed, then subsequent admissions/ presentations were censored. If the first readmission was negative for type 1 MI or biomarker evaluation, then subsequent presentations with biomarker positive chest pain was adjudicated until a MACE (Major Adverse cardiac event)

was defined or presentations were exhausted. It is important to note that nationally not all hospitals utilised high sensitivity troponins. (table 3 appendix details all hospital with troponins used [for adjudication] with representation with a possible MI).

We did not apply sex specific cut-offs to HSTnT. This was not the practise in our institute and recent evidence suggests limited value and consequence to this approach using this HSTn T assay.[14]

For all coronary revascularisations (surgical or percutaneous) a single consultant cardiologist adjudicated (by reference to discharge letters, review of coronary angiograms, biochemistry, biomarkers status) if an attempt at revascularisation (coronary artery bypass surgery or percutaneous coronary artery intervention) did occur and if so whether it fulfilled criteria for unplanned coronary revascularisation. (defined as hospital admission with unstable angina/ acute coronary syndrome, deemed to require inpatient revascularisation inclusive of primary percutaneous coronary interventions). As a case ascertainment exercise all national codes for coronary revascularisation were compared to in-house linkage for any revascularisation at the local tertiary centre for revascularisation. An additional 2 cases of urgent/ emergency revascularisation were identified by this exercise (that had been miscoded as non-coronary surgical intervention). Contentious outcomes based on coronary revascularisation underwent adjudication by an endpoint committee. (AK, PC, LM, FF)

Non-MI adjudication in index admission

Researchers were asked separately to diagnose non-MI diagnoses using all available information at index admission. The criteria for agreed and prespecified (drop-down) field settings.

Unstable Angina: Patients with normal cardiac troponin levels and typical angina at rest, a deterioration of a previously stable angina and in cases of positive cardiac exercise testing or cardiac catheterization with coronary arteries found to have a stenosis of 70% or greater.

Atypical Chest Pain: 2/3 features fulfilled for NICE criteria of ischaemic chest pain [15]

Cardiac Non-Coronary Chest pain: Convincing cardiac pathology with evidence for non-coronary disease; eg pericarditis, myocarditis, arrhythmia related

Non-cardiac Chest Pain: musculoskeletal pain, gastroesophageal disorder, pulmonary embolism or other causes of noncardiac chest pain

Chest pain of unknown origin: If diagnosis remained uncertain or insufficient diagnostic procedures/tests were performed

Appendix: supplementary tables and figures

Table 1: Patients with False negative HEART ≤3 and HSTnT limit of Detection at 6 weeks – details of presentation and major adverse cardiac events

Age	Gender	HEART score	Heart score criteria	Presentation ECG	HstnT 1	HStnT 2	Timing of HSTN T: CP to HS tn T	Cause of death	Additional descriptor	ICD code	MACE Event
False Negative HEART score ≤3											
61	male	3	Age (1), RF: smoking (1), moderately suspicious CP (1)	SR, non-ischaemic	6		40hr 25 mins	N/A	Readmission with MI (Hstn T 87, 117) 16 days following discharge	R073 (pain in chest wall)	**Subseq-uent MI**
93	female	3	Age (2), hstn T (1)	SR, 1st degree HB, non-ischaemic	19	33	5hr 8 mins	N/A	Index MI (3rd adjudicator involved)	R073	**Index MI**
51	male	3	Pvd (2), age (1)	Sinus rhythm, non-ischaemia	8		16hrs 30 mins	1. Gastrointestinal bleed secondary alcohol excess 2. Acute liver failure	Clear non-cardiac cause - index admission death	K720 (acute hepatic failure)	**Non-cardiac Death**
55	female	2	Age (1), hypertension (1)	SR, non-ischaemic	9	2	1hr 18 mins	Lung adenocarcinoma with bony metastases	Clear non-cardiac cause, index admission death	C349,M8250 /3	**Non-cardiac Death**
69	male	3	Age (2), RFs: smoking, hypertension (1)	SR, non-ischaemic	10		50hr 45 minutes	Small cell carcinoma of lung	Died at home 3 days after discharge	C349 M8041/3	**Non-cardiac Death**
False negative high sensitivity troponin T (LOD) and non-ischaemic ECG											
65	male	4	Age (2),risk factors (1), moderately suspicious CP (1)	SR, non-ischaemic	3	18	314minutes	N/A	Index MI	RO72 (central chest pain	**Index MI**

Abbreviations: SR= sinus rhythm, Hstn T= high sensitivity troponin T, ECG= electrocardiogram, MI= myocardial Infarction, PVD= peripheral vascular disease, ICD = international classification of disease, CP= Chest pain, N/A = not applicable, LOD= limit of detection

Table 2a: ICD 10 Revascularisation codes used

CLINICAL_CODE	CODE_SET_ID	VERSION	SHORT_DESC	LONG_DESC	OPCS_VERSION
K40	OPCS	4	SAPHENOUS VEIN GRAFT REPLACEME	SAPHENOUS VEIN GRAFT REPLACEMENT OF CORONARY ARTERY	4.2
K401	OPCS	4	Saphenous vein graft replaceme	Saphenous vein graft replacement of one coronary artery	4.2
K4010	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B11	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B14	OPCS	4	CORONARY BYPASS GRAFTS - ENDO	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B16	OPCS	4	REPAIR ASC. AORTA & COR. BYPAS	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B17	OPCS	4	REPAIR AORTIC ANEURYSM & BYPAS	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B18	OPCS	4	CABG & OTHER MAJOR CARDIAC (EG	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B1A	OPCS	4	TMR & CABG	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B1B	OPCS	4	CABG & CAROTID ENDARTERECTOMY	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B1C	OPCS	4	CABG & ABDOMINAL AORTIC ANEURY	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B21	OPCS	4	REPLACEMENT/REPAIR OF VALVE(S)	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B22	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K4010B23	OPCS	4	COMPOSITE REPL AORTA,VALVE + C	SAPHENOUS VEIN GRAFT REPLACEMENT OF ONE CORONARY ARTERY	4.2
K402	OPCS	4	Saphenous vein graft replaceme	Saphenous vein graft replacement of two coronary arteries	4.2
K4020	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B11	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B14	OPCS	4	CORONARY BYPASS GRAFTS - ENDO	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B16	OPCS	4	REPAIR ASC. AORTA & COR. BYPAS	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B17	OPCS	4	REPAIR AORTIC ANEURYSM & BYPAS	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B18	OPCS	4	CABG & OTHER MAJOR CARDIAC (EG	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B1A	OPCS	4	TMR & CABG	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B1B	OPCS	4	CABG & CAROTID ENDARTERECTOMY	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B1C	OPCS	4	CABG & ABDOMINAL AORTIC ANEURY	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B21	OPCS	4	REPLACEMENT/REPAIR OF VALVE(S)	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B22	OPCS	4	CABG + AVR + Carotid Endartere	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B23	OPCS	4	COMPOSITE REPL AORTA,VALVE + C	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K4020B32	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF TWO CORONARY ARTERIES	4.2
K403	OPCS	4	Saphenous vein graft replaceme	Saphenous vein graft replacement of three coronary arteries	4.2
K4030	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B11	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B14	OPCS	4	CORONARY BYPASS GRAFTS - ENDO	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B16	OPCS	4	REPAIR ASC. AORTA & COR. BYPAS	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B18	OPCS	4	CABG & OTHER MAJOR CARDIAC (EG	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B1A	OPCS	4	TMR & CABG	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B1B	OPCS	4	CABG & CAROTID ENDARTERECTOMY	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B1C	OPCS	4	CABG & ABDOMINAL AORTIC ANEURY	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B21	OPCS	4	REPLACEMENT/REPAIR OF VALVE(S)	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B22	OPCS	4	CABG + AVR + Carotid Endartere	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2

K4030B23	OPCS	4	COMPOSITE REPL AORTA,VALVE + C	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K4030B42	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF THREE CORONARY ARTERIES	4.2
K404	OPCS	4	Saphenous vein graft replaceme	Saphenous vein graft replacement of four or more coronary ar	4.2
K4040	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF FOUR OR MORE CORONARY AR	4.2
K4040B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B11	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B14	OPCS	4	CORONARY BYPASS GRAFTS - ENDO	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B16	OPCS	4	REPAIR ASC. AORTA & COR. BYPAS	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B18	OPCS	4	CABG & OTHER MAJOR CARDIAC (EG	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B1A	OPCS	4	TMR & CABG	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B1B	OPCS	4	CABG & CAROTID ENDARTERECTOMY	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B21	OPCS	4	REPLACEMENT/REPAIR OF VALVE(S)	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B22	OPCS	4	CABG + AVR + CAROTID ENDARTERE	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B23	OPCS	4	COMPOSITE REPL AORTA,VALVE + C	SAPHENOUS VEIN GRAFT REPLACE FOUR OR MORE CORONARY ARTERIES	4.2
K4040B52	OPCS	4	Coronary Artery Bypass Grafts	SAPHENOUS VEIN GRAFT REPLACEMENT OF FOUR OR MORE CORONARY AR	4.2
K408	OPCS	4	Other specified saphenous vein	Other specified saphenous vein graft replacement of coronary	4.2
K409	OPCS	4	Unspecified saphenous vein gra	Unspecified saphenous vein graft replacement of coronary art	4.2
K41	OPCS	4	OTHER AUTOGRAFT REPLACEMENT OF	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY	4.2
K411	OPCS	4	Autograft replacement of one c	Autograft replacement of one coronary artery NEC	4.2
K4110	OPCS	4	CABG + AVR + Carotid Endartere	AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC	4.2
K4110B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC	4.2
K4110B11	OPCS	4	Coronary Artery Bypass Grafts	AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC	4.2
K4110B1A	OPCS	4	TMR & CABG	AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC	4.2
K4110B21	OPCS	4	AUTO REPLACE ONE CON ART	AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC	4.2
K4110B22	OPCS	4	CABG + AVR + Carotid Endartere	AUTOGRAFT REPLACEMENT OF ONE CORONARY ARTERY NEC	4.2
K412	OPCS	4	Autograft replacement of two c	Autograft replacement of two coronary arteries NEC	4.2
K4120	OPCS	4	CABG + AVR + Carotid Endartere	AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC	4.2
K4120B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC	4.2
K4120B11	OPCS	4	Coronary Artery Bypass Grafts	AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC	4.2
K4120B1A	OPCS	4	TMR & CABG	AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC	4.2
K4120B21	OPCS	4	AUTO REPLACE TWO CON ART	AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC	4.2
K4120B22	OPCS	4	CABG + AVR + Carotid Endartere	AUTOGRAFT REPLACEMENT OF TWO CORONARY ARTERIES NEC	4.2
K413	OPCS	4	Autograft replacement of three	Autograft replacement of three coronary arteries NEC	4.2
K4130	OPCS	4	CABG + AVR + Carotid Endartere	AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC	4.2
K4130B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC	4.2
K4130B11	OPCS	4	Coronary Artery Bypass Grafts	AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC	4.2
K4130B1A	OPCS	4	TMR & CABG	AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC	4.2
K4130B21	OPCS	4	AUTO REPLACE THREE CON ART	AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC	4.2
K4130B22	OPCS	4	CABG + AVR + Carotid Endartere	AUTOGRAFT REPLACEMENT OF THREE CORONARY ARTERIES NEC	4.2
K414	OPCS	4	Autograft replacement of four	Autograft replacement of four or more coronary arteries NEC	4.2
K4140	OPCS	4	CABG + AVR + Carotid Endartere	AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC	4.2
K4140B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC	4.2
K4140B11	OPCS	4	Coronary Artery Bypass Grafts	AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC	4.2
K4140B1A	OPCS	4	TMR & CABG	AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC	4.2
K4140B21	OPCS	4	AUTO REPLACE FOUR > CON ART	AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC	4.2

K4140B22	OPCS	4	CABG + AVR + Carotid Endartere	AUTOGRAFT REPLACEMENT OF FOUR OR MORE CORONARY ARTERIES NEC	4.2
K418	OPCS	4	Other specified other autograf	Other specified other autograft replacement of coronary arte	4.2
K4180	OPCS	4	TMR & CABG	OTHER SPECIFIED	4.2
K4180B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY OS	4.2
K4180B11	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY OS	4.2
K4180B1A	OPCS	4	TMR & CABG	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY OS	4.2
K419	OPCS	4	Unspecified other autograft re	Unspecified other autograft replacement of coronary artery	4.2
K4190	OPCS	4	TMR & CABG	UNSPECIFIED	4.2
K4190B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY UNSPECIFIED	4.2
K4190B11	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY UNSPECIFIED	4.2
K4190B1A	OPCS	4	TMR & CABG	OTHER AUTOGRAFT REPLACEMENT OF CORONARY ARTERY UNSPECIFIED	4.2
K42	OPCS	4	ALLOGRAFT REPLACEMENT OF CORON	ALLOGRAFT REPLACEMENT OF CORONARY ARTERY	4.2
K421	OPCS	4	Allograft replacement of one c	Allograft replacement of one coronary artery	4.2
K422	OPCS	4	Allograft replacement of two c	Allograft replacement of two coronary arteries	4.2
K423	OPCS	4	Allograft replacement of three	Allograft replacement of three coronary arteries	4.2
K424	OPCS	4	Allograft replacement of four	Allograft replacement of four or more coronary arteries	4.2
K428	OPCS	4	Other specified allograft repl	Other specified allograft replacement of coronary artery	4.2
K429	OPCS	4	Unspecified allograft replacem	Unspecified allograft replacement of coronary artery	4.2
K43	OPCS	4	PROSTHETIC REPLACEMENT OF CORO	PROSTHETIC REPLACEMENT OF CORONARY ARTERY	4.2
K431	OPCS	4	Prosthetic replacement of one	Prosthetic replacement of one coronary artery	4.2
K432	OPCS	4	Prosthetic replacement of two	Prosthetic replacement of two coronary arteries	4.2
K433	OPCS	4	Prosthetic replacement of thre	Prosthetic replacement of three coronary arteries	4.2
K434	OPCS	4	Prosthetic replacement of four	Prosthetic replacement of four or more coronary arteries	4.2
K438	OPCS	4	Other specified prosthetic rep	Other specified prosthetic replacement of coronary artery	4.2
K439	OPCS	4	Unspecified prosthetic replace	Unspecified prosthetic replacement of coronary artery	4.2
K44	OPCS	4	OTHER REPLACEMENT OF CORONARY	OTHER REPLACEMENT OF CORONARY ARTERY	4.2
K441	OPCS	4	Replacement of coronary arteri	Replacement of coronary arteries using multiple methods	4.2
K442	OPCS	4	Revision of replacement of cor	Revision of replacement of coronary artery	4.2
K4420	OPCS	4	POST OP ATTENTION TO GRAFTS -	REVISION OF REPLACEMENT OF CORONARY ARTERY	4.2
K4420B15	OPCS	4	POST OP ATTENTION TO GRAFTS -	REVISION OF REPLACEMENT OF CORONARY ARTERY	4.2
K448	OPCS	4	Other specified other replacem	Other specified other replacement of coronary artery	4.2
K449	OPCS	4	Unspecified other replacement	Unspecified other replacement of coronary artery	4.2
K451	OPCS	4	Double anastomosis of mammary	Double anastomosis of mammary arteries to coronary arteries	4.2
K4510B10	OPCS	4	DOUBLE ANASTOMOSIS OF MAMMARY	DOUBLE ANASTOMOSIS OF MAMMARY ARTERIES TO CORONARY ARTERIES	4.2
K4510B11	OPCS	4	DOUBLE ANASTOMOSIS OF MAMMARY	DOUBLE ANASTOMOSIS OF MAMMARY ARTERIES TO CORONARY ARTERIES	4.2
K4510B21	OPCS	4	CABG WITH VALVE REPAIR	DOUBLE ANASTOMOSIS OF MAMMARY ARTERIES TO CORONARY ARTERIES	4.2
K452	OPCS	4	Double anastomosis of thoracic	Double anastomosis of thoracic arteries to coronary arteries	4.2
K453	OPCS	4	Anastomosis of mammary artery	Anastomosis of mammary artery to left anterior descending co	4.2
K4530	OPCS	4	Coronary Artery Bypass Grafts	ANASTOMOSIS OF MAMMARY ARTERY TO LEFT ANTERIOR DESCENDING CO	4.2
K4530B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B11	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B13	OPCS	4	MIDCAB-MIN INVASIVE BYPASS GRA	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B14	OPCS	4	CORONARY BYPASS GRAFTS - ENDO	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B16	OPCS	4	REPAIR ASC. AORTA & COR. BYPAS	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B18	OPCS	4	CABG & OTHER MAJOR CARDIAC (EG	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2

K4530B1A	OPCS	4	TMR & CABG	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B1B	OPCS	4	CABG & CAROTID ENDARTERECTOMY	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B21	OPCS	4	REPLACEMENT/REPAIR OF VALVE(S)	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B22	OPCS	4	CABG + AVR + CAROTID ENDARTERE	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B23	OPCS	4	COMPOSITE REPL AORTA,VALVE + C	ANAST MAMMARY ARTERY TO LT ANTERIOR DESCENDING CORON ARTERY	4.2
K4530B62	OPCS	4	Coronary Artery Bypass Grafts	ANASTOMOSIS OF MAMMARY ARTERY TO LEFT ANTERIOR DESCENDING CO	4.2
K454	OPCS	4	Anastomosis of mammary artery	Anastomosis of mammary artery to coronary artery NEC	4.2
K4540	OPCS	4	Coronary Artery Bypass Grafts	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B10	OPCS	4	CORONARY ARTERY BYPASS GRAFTS	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B11	OPCS	4	Coronary Artery Bypass Grafts	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B12	OPCS	4	Coronary Artery Bypass Grafts	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B14	OPCS	4	CORONARY BYPASS GRAFTS - ENDO	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B16	OPCS	4	REPAIR ASC. AORTA & COR. BYPAS	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B18	OPCS	4	CABG & OTHER MAJOR CARDIAC (EG	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B1A	OPCS	4	TMR & CABG	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B1B	OPCS	4	CABG & CAROTID ENDARTERECTOMY	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B21	OPCS	4	REPLACE/REPAIR VALVE(S) & CABG	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B22	OPCS	4	CABG + AVR + Carotid Endartere	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K4540B23	OPCS	4	COMPOSITE REPL AORTA,VALVE + C	ANASTOMOSIS OF MAMMARY ARTERY TO CORONARY ARTERY NEC	4.2
K455	OPCS	4	Anastomosis of thoracic artery	Anastomosis of thoracic artery to coronary artery NEC	4.2
K456	OPCS	4	Revision of connection of thor	Revision of connection of thoracic artery to coronary artery	4.2
K458	OPCS	4	Other specified connection of	Other specified connection of thoracic artery to coronary ar	4.2
K459	OPCS	4	Unspecified connection of thor	Unspecified connection of thoracic artery to coronary artery	4.2
K46	OPCS	4	OTHER BYPASS OF CORONARY ARTER	OTHER BYPASS OF CORONARY ARTERY	4.2
K463	OPCS	4	Implantation of mammary artery	Implantation of mammary artery into heart NEC	4.2
K468	OPCS	4	Other specified other bypass o	Other specified other bypass of coronary artery	4.2
K469	OPCS	4	Unspecified other bypass of co	Unspecified other bypass of coronary artery	4.2
K49	OPCS	4	TRANSLUMINAL BALLOON ANGIOPLAS	TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY	4.2
K491	OPCS	4	Percutaneous transluminal ball	Percutaneous transluminal balloon angioplasty of one coronar	4.2
K4910	OPCS	4	LASER ANGIOPLASTY - ONE BALLOO	PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY OF ONE CORONAR	4.2
K4910D11	OPCS	4	ABANDONED PTCA	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D12	OPCS	4	SIMPLE PTCA - ONE OR TWO BALLO	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D21	OPCS	4	SIMPLE PTCA-MORE THAN 2 BALLOO	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D34	OPCS	4	PTCA - ONE STENT & ONE BALLOON	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D35	OPCS	4	PTCA - 1 STENT, NO BALLOON	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D37	OPCS	4	LASER ANGIOPLASTY - ONE BALLOO	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D41	OPCS	4	PTCA - 2 OR MORE STENTS	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D42	OPCS	4	PTCA - 2 OR MORE STENTS, NO BA	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D44	OPCS	4	PTCA WITH STENT & ROTABLATOR	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D45	OPCS	4	PTCA WITH STENT - 2+ BALLOONS	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D49	OPCS	4	PTCA WITH 2+STENTS (2+ BALLOON	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D4B	OPCS	4	LASER ANGIOPLASTY, MORE THAN O	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K4910D4C	OPCS	4	LASER ANGIOPLASTY WITH STENT(S	PERCUT TRANSLUMINAL BALLOON ANGIOPLASTY ONE CORONARY ARTERY	4.2
K492	OPCS	4	Percutaneous transluminal ball	Percutaneous transluminal balloon angioplasty of multiple co	4.2
K4920	OPCS	4	PTCA with Stent & Rotablator	PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY OF MULTIPLE CO	4.2

K4920D11	OPCS	4	ABANDONED PTCA	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D12	OPCS	4	SIMPLE PTCA - ONE OR TWO BALLO	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D21	OPCS	4	SIMPLE PTCA-MORE THAN 2 BALLOO	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D34	OPCS	4	PTCA - ONE STENT & ONE BALLOON	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D35	OPCS	4	PTCA - 1 STENT, NO BALLOON	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D37	OPCS	4	LASER ANGIOPLASTY - 1 BALLOON	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D41	OPCS	4	PTCA - 2 OR MORE STENTS	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D42	OPCS	4	PTCA - 2 STENTS, NO BALLOON	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D44	OPCS	4	PTCA WITH STENT & ROTABLATOR	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D45	OPCS	4	PTCA WITH STENT - 2+ BALLOONS	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D49	OPCS	4	PTCA WITH 2+STENTS (2+ BALLOON	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D4B	OPCS	4	LASER ANGIOPLASTY - 1 BALLOON	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K4920D4C	OPCS	4	LASER ANGIOPLASTY WITH STENT(S	PERCUT TRANSLUM BALLOON ANGIOPLASTY MULITPLE CORON ARTERIES	4.2
K493	OPCS	4	Percutaneous transluminal ball	Percutaneous transluminal balloon angioplasty of bypass graf	4.2
K4930	OPCS	4	PTCA with Stent & Rotablator	PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY OF BYPASS GRAF	4.2
K4930D12	OPCS	4	SIMPLE PTCA - ONE OR TWO BALLO	PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART	4.2
K4930D21	OPCS	4	SIMPLE PTCA-MORE THAN 2 BALLOO	PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART	4.2
K4930D34	OPCS	4	PTCA - ONE STENT & ONE BALLOON	PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART	4.2
K4930D35	OPCS	4	PTCA - 1 STENT, NO BALLOON	PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART	4.2
K4930D41	OPCS	4	PTCA - 2 OR MORE STENTS	PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART	4.2
K4930D44	OPCS	4	PTCA WITH STENT & ROTABLATOR	PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART	4.2
K4930D45	OPCS	4	PTCA WITH STENT - 2+ BALLOONS	PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART	4.2
K4930D49	OPCS	4	PTCA WITH 2+STENTS (2+ BALLOON	PERCUT TRANSLUM BALLOON ANGIOPLASTY BYPASS GRAFT CORON ART	4.2
K494	OPCS	4	Percutaneous transluminal cutt	Percutaneous transluminal cutting balloon angioplasty of cor	4.2
K498	OPCS	4	Other specified transluminal b	Other specified transluminal balloon angioplasty of coronary	4.2
K4980	OPCS	4	PTCA with Stent & Rotablator	OTHER SPECIFIED	4.2
K4980D34	OPCS	4	PTCA - ONE STENT & ONE BALLOON	TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS	4.2
K4980D41	OPCS	4	PTCA - 2 OR MORE STENTS	TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS	4.2
K4980D44	OPCS	4	PTCA WITH STENT & ROTABLATOR	TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS	4.2
K4980D45	OPCS	4	PTCA WITH STENT - 2+ BALLOONS	TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS	4.2
K4980D49	OPCS	4	PTCA WITH 2+STENTS (2+ BALLOON	TRANSLUMINAL BALLOON ANGIOPLASTY OF CORONARY ARTERY OS	4.2
K499	OPCS	4	Unspecified transluminal ballo	Unspecified transluminal balloon angioplasty of coronary art	4.2
K50	OPCS	4	OTHER THERAPEUTIC TRANSLUMINAL	OTHER THERAPEUTIC TRANSLUMINAL OPERATIONS ON CORONARY ARTERY	4.2
K501	OPCS	4	Percutaneous transluminal lase	Percutaneous transluminal laser coronary angioplasty	4.2
K5010	OPCS	4	LASER ANGIOPLASTY - NO BALLOON	PERCUTANEOUS TRANSLUMINAL LASER CORONARY ANGIOPLASTY	4.2
K5010D36	OPCS	4	LASER ANGIOPLASTY - NO BALLOON	PERCUTANEOUS TRANSLUMINAL LASER CORONARY ANGIOPLASTY	4.2
K502	OPCS	4	Percutaneous transluminal coro	Percutaneous transluminal coronary thrombolysis using strept	4.2
K503	OPCS	4	Percutaneous transluminal inje	Percutaneous transluminal injection of therapeutic substance	4.2
K504	OPCS	4	Percutaneous transluminal athe	Percutaneous transluminal atherectomy of coronary artery	4.2
K508	OPCS	4	Other specified other therapeu	Other specified other therapeutic transluminal operations on	4.2
K5080	OPCS	4	PTCA with Rota -1 balloon,1 or	PTDA	4.2
K5080D31	OPCS	4	PTCA WITH ROTA -1 BALLOON,1 OR	OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS	4.2
K5080D32	OPCS	4	CORONARY TEC - ONE BALLOON	OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS	4.2
K5080D33	OPCS	4	DCA - ONE BALLOON	OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS	4.2
K5080D43	OPCS	4	PTCA-2 OR MORE ROTABLATORS	OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS	4.2

K5080D44	OPCS	4	PTCA WITH STENT & ROTABLATOR	OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS	4.2
K5080D46	OPCS	4	PTCA WITH ROTABLATOR - 2+ BALL	OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS	4.2
K5080D47	OPCS	4	CORONARY TEC - 2+ BALLOONS	OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS	4.2
K5080D48	OPCS	4	DCA - 2+BALLOONS	OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS	4.2
K5080D4A	OPCS	4	CORONARY TEC WITH STENT(S) INC	OTHER THERAP TRANSLUMINAL OPERATIONS ON CORONARY ARTERY OS	4.2
K509	OPCS	4	Unspecified other therapeutic	Unspecified other therapeutic transluminal operations on coronary artery	4.2
K75	OPCS	4	PERCUTANEOUS TRANSLUMINAL BALL	PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY AND STENTING O	4.2
K751	OPCS	4	Percutaneous transluminal ball	Percutaneous transluminal balloon angioplasty and insertion	4.2
K752	OPCS	4	Percutaneous transluminal ball	Percutaneous transluminal balloon angioplasty and insertion	4.2
K753	OPCS	4	Percutaneous transluminal ball	Percutaneous transluminal balloon angioplasty and insertion	4.2
K754	OPCS	4	Percutaneous transluminal ball	Percutaneous transluminal balloon angioplasty and insertion	4.2
K758	OPCS	4	Other specified percutaneous t	Other specified percutaneous transluminal balloon angioplasty	4.2
K759	OPCS	4	Unspecified percutaneous trans	Unspecified percutaneous transluminal balloon angioplasty an	4.2

Table 2b: ICD 10 codes used to identify type 1 myocardial infarctions

CLINICAL_CODE	CODE_SET_ID	VERSION	SHORT_DESC	LONG_DESC
I20	ICD	10	Angina pectoris	Angina pectoris
I200	ICD	10		UNSTABLE ANGINA
I201	ICD	10		ANGINA PECTORIS WITH DOCUMENTED SPASM
I208	ICD	10		OTHER FORMS OF ANGINA PECTORIS
I209	ICD	10		ANGINA PECTORIS, UNSPECIFIED
I21	ICD	10	Acute myocardial infarction	Acute myocardial infarction
I210	ICD	10		ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF ANTERIOR WALL
I211	ICD	10		ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF INFERIOR WALL
I212	ICD	10		ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF OTHER SITES
I213	ICD	10		ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF UNSPECIFIED SITE
I214	ICD	10		ACUTE SUBENDOCARDIAL MYOCARDIAL INFARCTION
I219	ICD	10		ACUTE MYOCARDIAL INFARCTION, UNSPECIFIED
I22	ICD	10	Subsequent myocardial infarction	Subsequent myocardial infarction
I220	ICD	10		SUBSEQUENT MYOCARDIAL INFARCTION OF ANTERIOR WALL
I221	ICD	10		SUBSEQUENT MYOCARDIAL INFARCTION OF INFERIOR WALL
I228	ICD	10		SUBSEQUENT MYOCARDIAL INFARCTION OF OTHER SITES
I229	ICD	10		SUBSEQUENT MYOCARDIAL INFARCTION OF UNSPECIFIED SITE
I24	ICD	10	Other acute ischaemic heart disease	Other acute ischaemic heart disease
I240	ICD	10		CORONARY THROMBOSIS NOT RESULTING IN MYOCARDIAL INFARCTION
I241	ICD	10		DRESSLER'S SYNDROME
I248	ICD	10		OTHER FORMS OF ACUTE ISCHAEMIC HEART DISEASE
I249	ICD	10		ACUTE ISCHAEMIC HEART DISEASE, UNSPECIFIED
I25	ICD	10	Chronic ischaemic heart disease	Chronic ischaemic heart disease
I250	ICD	10		ATHEROSCLEROTIC CARDIOVASCULAR DISEASE, SO DESCRIBED
I251	ICD	10		ATHEROSCLEROTIC HEART DISEASE
I253	ICD	10		ANEURYSM OF HEART
I254	ICD	10		CORONARY ARTERY ANEURYSM
I255	ICD	10		ISCHAEMIC CARDIOMYOPATHY

I256	ICD	10		SILENT MYOCARDIAL ISCHAEMIA
I46	ICD	10	Cardiac arrest	Cardiac arrest
I460	ICD	10		CARDIAC ARREST WITH SUCCESSFUL RESUSCITATION
I461	ICD	10		SUDDEN CARDIAC DEATH, SO DESCRIBED
I469	ICD	10		CARDIAC ARREST, UNSPECIFIED
R071	ICD	10		CHEST PAIN ON BREATHING
R072	ICD	10		PRECORDIAL PAIN
R073	ICD	10		OTHER CHEST PAIN
R074	ICD	10		CHEST PAIN, UNSPECIFIED
R96	ICD	10	Other sudden death, cause unkn	Other sudden death, cause unkn
R960	ICD	10		INSTANTANEOUS DEATH
R961	ICD	10		DEATH OCCURRING LESS THAN 24 HOURS FROM ONSET OF SYMPTOMS, N
R98X	ICD	10		UNATTENDED DEATH
R99X	ICD	10		OTHER ILL-DEFINED AND UNSPECIFIED CAUSES OF MORTALITY

Table 3 Re-presentation (up to 1 year following index discharge) to English hospitals with any ischaemic heart disease or coronary revascularisation code: troponin assays in use and reference ranges

Hospital	Assay	Manufacturer	High sensitive assay	Reference range	Units
St Helens and Knowsley NHS trust	Troponin I	Siemens	No	≤0.05	micrograms/l
East Cheshire Hospital NHS trust	TroponinI	Beckman	Yes	<34	nanograms/l
Southport hospital NHS Trust	Troponin T	Roche	yes	<15	nanograms/l
Warrington Hospital NHS Trust	Troponin I	Siemens	no	<0.03	Micrograms/l
University hospital Aintree NHS Foundation Trust	Troponin T	Roche	yes	<15	nanograms/l
Royal Liverpool Hospitals	Troponin T	Roche	yes	<15	nanograms/l
Liverpool Heart and Chest hospital NHS foundation trust	Troponin T	Roche	yes	<15	nanograms/l
Pilgrim Hospital	Troponin T	Roche	Yes	<15 (female) <10 (male)	nanograms/l

Table 4 Inter-observer variability in risk score determination

Risk SCORE	Inter-observer variability in determination of risk scores		
	Absolute	Risk category*	
	Agreement	Agreement	κ
HEART	16/18 (89%)	18/18 (100%)	1.0
TIMI	13/18 (72%)	18/18 (100%)	1.0
GRACE	11/18 (61%)	17/18 (94%)	0.82

*agreement of risk category determination (low, intermediate, high risk score determination of each risk score)

Table 5 Interaction of timing of high sensitivity troponin T check relative to CP onset and outcome (MACE)

Rule-Out Protocol	**Chest pain (peak) to first troponin Check (hours) (n-discharged, npv with confidence intervals at 42 days)**					
	<3	≥3	P value	<6	≥6	P value
HStnT <15 and nonischaemic ECG	40 (0.976 (0.871 – 0.999))	913 (0.983 (0.972-0.990))	0.563	128 (0.985 (0.946-0.998))	825 (0.982 (0.971-0.990))	1.000
HsTnt <5 and nonischaemic ECG	23 (1.000 (0.852 – 1.000))	579 (0.998 (0.990 – 1.000)	1.000	71 (1.000 (0.949-1.000))	531 (0.998 (0.990-1.000))	1.000
HEART ≤3	36 (1.000 (0.903-1.000))	831 (0.994 (0.986-0.998)	1.000	101 (0.990 (0.947-1.000))	766 (0.995 (0.987-0.999))	0.464
TIMI≤1	40 (0.976 (0.871-0.999))	867 (0.980 (0.968-0.988))	0.581	116 (0.959 (0.906-0.986))	791 (0.983 (0.971-0.990))	0.090
GRACE ≤75	25 (0.962 (0.804 – 0.999))	433 (0.982 (0.965-0.992))	0.406	65 (0.970 (0.896-0.996))	393 (0.983 (0.964-0.993))	0.623

Abbreviations: NPV= negative predictive value

Figure 1: Negative and Positive predictive values for MACE (type 1 myocardial infarction, unplanned coronary revascularisation and all cause death) at 6 weeks according to rule-out strategies (dashed lines represents 99% NPV)

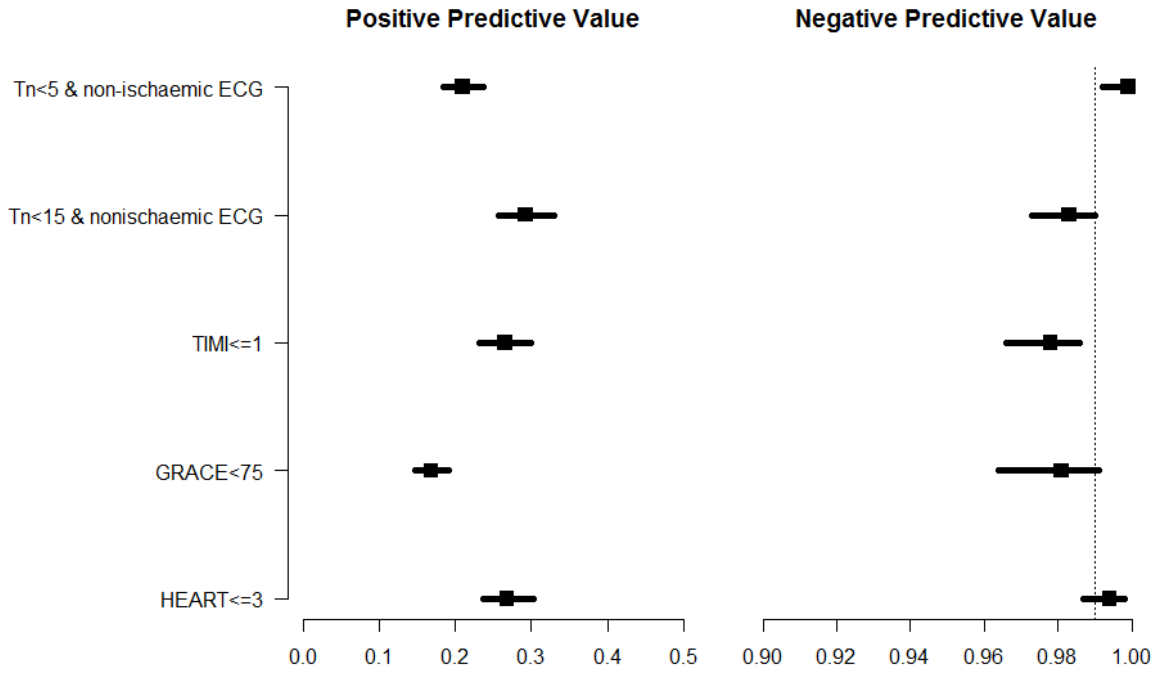
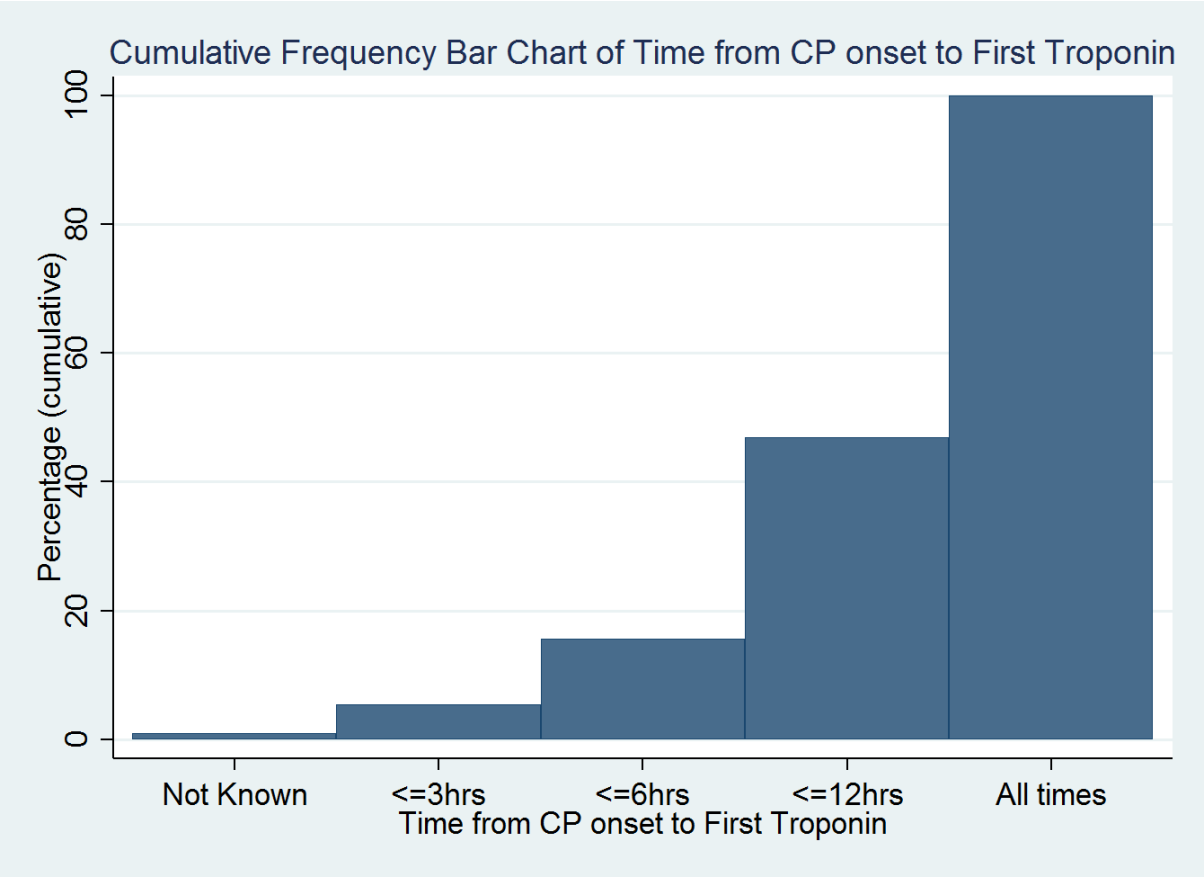


Figure 2: Time of chest pain to first High sensitivity troponin T sampling



Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1, 2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	5
	4	Study objectives and hypotheses	2, 5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5, 6
Participants	**6**	Eligibility criteria	4,5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	4, 5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	2, 4, 5
Test methods	**10a**	Index test, in sufficient detail to allow replication	5, 6, 10
	10b	Reference standard, in sufficient detail to allow replication	3,4 (appendix)
	11	Rationale for choosing the reference standard (if alternatives exist)	3, 4(appendix)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	2,3,4 (appendix)
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	2,3,4(appendix)
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	3, 4(appendix)
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	3,4 (appendix)
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7, 8
	15	How indeterminate index test or reference standard results were handled	3 (appendix)
	16	How missing data on the index test and reference standard were handled	N/A
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	7
	18	Intended sample size and how it was determined	7, 8
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Figure 1
	20	Baseline demographic and clinical characteristics of participants	Table 1, page 22
	21a	Distribution of severity of disease in those with the target condition	Table 1, page 22
	21b	Distribution of alternative diagnoses in those without the target condition	9
	22	Time interval and any clinical interventions between index test and reference standard	Figure 2 (appendix)
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 2, table 1 (appendix)
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 2
	25	Any adverse events from performing the index test or the reference standard	N/A
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	14, 15
	27	Implications for practice, including the intended use and clinical role of the index test	13
OTHER INFORMATION			
	28	Registration number and name of registry	3
	29	Where the full study protocol can be accessed	3
	30	Sources of funding and other support; role of funders	3

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.